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PRE-APPEAL BRIEF REQUEST FOR REVIEW	Docket Number (Optional) EINAT1.1D	
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 14550, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]	Application Number 10/091,333	Filed March 6, 2002
on _____	First Named Inventor Paz EINAT	
Signature _____		
Typed or printed name _____	Art Unit 1635	Examiner B. A. Whiteman

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☒ attorney of record. Registration number 25,618.
- ☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

/rlb/
Signature

Roger L. Browdy
Typed or Printed Name

202-628-5197
Telephone number

May 14, 2007
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

REASONS WHY REVIEW IS REQUESTED

In the advisory action of April 25, 2007, the examiner stated that, for the purposes of appeal, applicant's amendment of April 16, 2007, would be entered, but that all of claims 17, 20 21 and 40 remain rejected. All of the claims are subject to two rejections. One is a 35 U.S.C. 112, first paragraph, written description-new matter rejection and the other is a 325 U.S.C. 112, first paragraph, written description rejection on the grounds that the specification fails to reasonably convey that the inventors had possession of the claimed invention at the time that the application was filed.

With respect to the new matter rejection, it is apparently the examiner's position that there is no support in the specification that the antisense molecule targets the nucleotide sequence encoding the amino acid sequence of SEQ ID NO:10. However, the concept of using a nucleotide sequence encoding a polypeptide having the amino acid of SEQ ID NO:10 as the target for the antisense molecule is indeed supported by the specification. Paragraph [0050] states that the invention provides a method of regulating angiogenesis in a patient in need of such treatment by administering to a patient "a therapeutically effective amount of an antagonist of at least one protein as encoded by the nucleic acid sequences as set forth in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6." The last sentence of this same paragraph reads:

> The antagonizing step can include blocking cellular receptors for the gene products of SEQ ID NOs:1-6 and can include antisense treatment as discussed hereinbelow. [Emphasis added]

Therefore, it is clear that antisense treatment is one specific example of the antagonist treatment referred to in paragraph [0050].

Paragraph [0052] further relates to the method of the present invention for regulating angiogenesis or apoptosis or for regulating response to hypoxic conditions in a patient in need of such treatment by administering a "an antisense oligonucleotide directed against at least one of the

sequences set forth in the group comprising SEQ ID NO:1; SEQ ID NO:2; SEQ ID NO:3; SEQ ID NO:4; SEQ ID NO:5; and SEQ ID NO:6." (See page 22, lines 6-9).

Paragraph [0125], beginning at line 8 of page 55 of the specification, states:

> SEQ ID NO:1 (RTP801) is the rat homolog of SEQ ID NO:2 (human RTP779). The protein sequences are SEQ ID NO:9 and SEQ ID NO:10 respectively.

Thus, it is clear that SEQ ID NO:10 is the protein sequence encoded by SEQ ID NO:2. Accordingly, reference to SEQ ID NO:2 in paragraph [0052] (and elsewhere) is effectively a reference to the DNA encoding SEQ ID NO:10.

Paragraph [0054] states that the invention further relates to the method for the treatment of a subject in need of treatment for hypoxia or ischemia-related disease (such as stroke) by administering a therapeutically amount of "an antagonist of a protein having a sequence as set forth in SEQ ID NO:10 ..." Thus, it is explicitly clear that SEQ ID NO:10 is a target for antagonist treatment. As discussed above, paragraph [0050] indicates that antisense treatment is a species of antagonist treatment. See also paragraph [0055] in this regard, where it further specifically refers to the use of an antagonist of a protein having a sequence as set forth in SEQ ID NO:10.

Paragraphs [0056] *et seq.* discuss antisense technology as is well known in the art, disclosing how to find appropriate inhibitory antisense oligonucleotides, including antisense mRNA, against any given a target sequence. As indicated above, SEQ ID NO:10, or nucleic acid encoding SEQ ID NO:10, is clearly a preferred target sequence and, thus, reference to SEQ ID NO:10 as the target sequence in claims 17 and 40, is not new matter.

Accordingly, upon review of this rejection, it should be clear that there is support for using mRNA encoding a polypeptide consisting of the amino acid sequence of SEQ ID NO:10 as the target sequence in defining complementary antisense RNA molecules.

With respect to the second written description rejection, this is essentially based on the examiner's position that it would take undue experimentation to determine which complements of at least seven nucleotides of target mRNA encoding a polypeptide consisting of the amino acid

sequence of SEQ ID NO:10 will be operable to result in prevention of processing, splicing, transport or translation of the mRNA or in mRNA degradation. In the advisory action of April 25, 2007, the examiner stated:

> In response to applicant's argument that antisense technology is well developed and the specification provides great detail about how the skilled artisan selects appropriate antisense molecules, the argument is not found persuasive because the art of record teaches that antisense has to be determined experimentally in practice .... The generic teaching in the specification of antisense technology, the lack of guidance in the specification for making the genus of antisense molecules recited in the instant claims and the art of record teaching that each antisense has to be determine[d] experimentally indicates that the applicant was not in possession of the claimed invention.

This written description rejection should be overturned prior to the necessity of applicants writing an appeal-brief, as the examiner has not followed the PTO's own training materials in this regard. Reference is made to "Synopsis of Application of Written Description Guidelines," which is in the nature of examiner training materials and is publicly available on the PTO website (http://www.uspto.gov/web/menu/written.pdf). Example 15 specifically relates to antisense claims very similar to those of the present invention. As in that Example, the present specification discloses a target oligonucleotide sequence, i.e., that encoding SEQ ID NO:10, as discussed above with respect to the previous rejection. The specification has support for the claimed function of the antisense, i.e., prevention of processing, splicing, transport or translation of the mRNA or in mRNA degradation (see page 23, line 24, to page 24, line 4, of the present specification). In Example 15, the specification described an art recognized method of screening for antisense molecules that is called "gene walking." The present specification goes even further in describing the computer program OLIGO, which can be used to estimate potential self-dimer formation and self-complementary properties and which provides an indication of whether any given fraction will have potential as an antisense molecule. Furthermore, in paragraph [0056], seven reviews are cited covering the main aspects of antisense technology, including the chemical, cellular and therapeutic aspects of antisense technology. Every one of these reviews are of record as

references in this case and have been incorporated by reference (see paragraph [0164]). Clearly, a reading of paragraphs [0056] though [0060] of the present specification makes clear that those complementary sequences with some potential or essentially complete potential can be readily determined and obviously they can each be readily tested for the specified properties.

In the analysis in Example 15, it was pointed out that the general knowledge in the art is that any full length complement of a target mRNA inhibits the function of the mRNA and is therefore an antisense oligonucleotide. In the present specification, as discussed hereinabove, SEQ ID NO:2 is the DNA that encodes the SEQ ID NO:10. The full length complement thereof will clearly be applicable as an antisense oligonucleotide and, thus, as in the Example 15 of the training materials, one of skill in the art would view applicant's disclosure of a coding sequence, with the statement that the invention includes antisense oligonucleotides, as an implicit disclosure that the full length complement of SEQ ID NO:2 is an antisense oligonucleotide. The guidelines further recognize that it is generally accepted in the art that oligonucleotides complementary to a messenger RNA, including fragments of the full length complement, have antisense activity when they match accessible regions on the target mRNA. This generally accepted knowledge is certainly present in the many reviews discussed in the present specification.

The training materials point out that the claim is drawn to the genus of antisense molecules that have the desired function with respect to the target sequence. There is a single species described with a complete structure, i.e., the full length complement. The guidelines recognize that the procedures for making oligonucleotide fragments of the full length complement are conventional, and the procedures for screening for antisense activity are conventional. Accordingly, the analysis in this example concludes:

> When considering the distinguishing characteristics of the claimed invention, the sequence provided in the specification defines and limits the structure of any effective antisense molecules. The specification also teaches the functional characteristics of the claimed invention as well as a routine art recognized method of making and screening for the claimed invention.

Thus, a conclusion is reached that the claimed invention is adequately described.

For the same reason the present claims are adequately described. As in Example 15 in the training materials, considering the specification's disclosure of:

(1) the sequence (SEQ ID NO:2, which encodes SEQ ID NO:10) which defines and limits the structure of any effective antisense molecules such that one skilled in the art would be able to immediately envisage members of the genus embraced by the claim, and

(2) the functional characteristics of the claimed invention as well as a routine art-recognized method of screening for antisense molecules that provide further distinguishing characteristics of the claimed invention, along with

(3) the general level of knowledge and skill in the art,

one skilled in the art would conclude that applicant was in possession of the invention.

The present specification does not purport to make any novel discoveries with respect to antisense technology. The antisense claims are based on the novelty of SEQ ID NO:10 and the well-known techniques of defining which complementary oligonucleotides will be operable. Accordingly, for the reasons discussed above, it is urged that these rejections be withdrawn following a pre-brief appeal conference and that this application be passed to allowance.

Respectfully submitted,

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